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PATENT

DOCKET NO.: ISIS-5207
Application No.: 10/701,236
Restriction Requirement Mailed: June 21, 2006

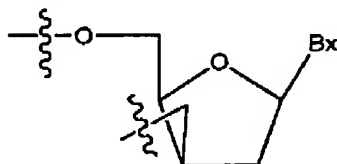
In the Claims:

The current status of all claims is listed below and supersedes all previous lists of claims.

1. (currently amended) A composition comprising a first oligomer and a second oligomer, wherein:
 - at least a portion of said first oligomer is capable of hybridizing with at least a portion of said second oligomer,
 - at least a portion of said first oligomer is complementary to and capable of hybridizing with a selected target nucleic acid, and
 - at least one of said first or said second oligomers includes at least one sugar surrogate wherein said sugar surrogate is a 4'-thioribonucleoside or a 2'-deoxy-4'-thioribonucleoside.
2. (original) The composition of claim 1 wherein said first and said second oligomers are a complementary pair of siRNA oligomers.
3. (original) The composition of claim 1 wherein said first and said second oligomers are an antisense/sense pair of oligomers.
4. (original) The composition of claim 1 wherein each of said first and second oligomers has 10 to 40 nucleobases.
5. (original) The composition of claim 1 wherein each of said first and second oligomers has 18 to 30 nucleobases.
6. (original) The composition of claim 1 wherein each of said first and second oligomers has 21 to 24 nucleobases.
7. (original) The composition of claim 1 wherein said first oligomer is an antisense oligomer.

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8. (original) The composition of claim 7 wherein said second oligomer is a sense oligomer.
9. (original) The composition of claim 7 wherein said second oligomer has a plurality of ribose nucleoside units.
10. (original) The composition of claim 1 wherein said first oligomer includes said sugar surrogate.
11. (withdrawn) The composition of claim 1 wherein the sugar surrogate is a cyclobutyl nucleoside, cyclopentyl nucleoside, proline nucleoside, cyclohexene nucleoside, hexose nucleoside or a cyclohexane nucleoside.
12. (withdrawn) The composition of claim 1 wherein the sugar surrogate is an arabinonucleoside, xylonucleoside, lyxonucleoside, erythronucleoside, threonucleoside, 4'-thioribonucleoside, or 2'-deoxy-4'-thioribonucleoside.
13. (withdrawn) The composition of claim 12 wherein the sugar surrogate is an arabinonucleoside.
14. (withdrawn) The composition of claim 12 wherein the sugar surrogate is an xylonucleoside of the formula:

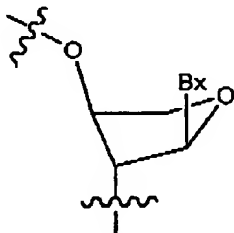


where Bx is a heterocyclic base moiety.

15. (withdrawn) The composition of claim 12 wherein the sugar surrogate is a threonucleoside of the formula:

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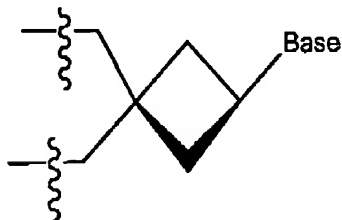
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wherein Bx is a hetrocyclic base moiety.

16. (withdrawn) The composition of claim 11 wherein the sugar surrogate is a cyclobutyl nucleoside.

17. (withdrawn) The composition of claim 16 wherein the cyclobutyl nucleoside is of the formula:



18 (withdrawn) The composition of claim 11 wherein the sugar surrogate is a cyclopentyl nucleoside.

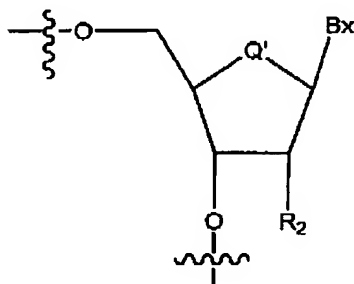
19 (withdrawn) The composition of claim 18 wherein the cyclopentyl nucleoside is of the formula:

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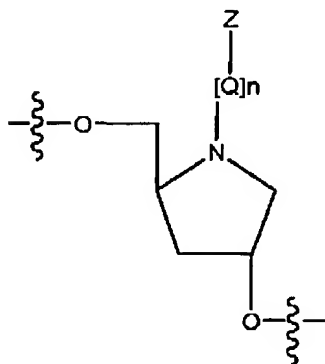
where:

Bx is a heterocyclic base moiety;

Q' is CH₂, CHF, or CF₂; andR₂ is sugar substituent.

20. (withdrawn) The composition of claim 11 wherein the sugar surrogate is a proline nucleoside.

21. (withdrawn) The composition of claim 20 wherein the proline nucleoside is of the formula:



wherein:

Z is L₈, L₈-G₁, L₉, L₉-G₂, NR₂₃R₂₄, a nitrogen-containing heterocycle, a purine, a pyrimidine, a phosphate group, a polyether group, or a polyethylene glycol group;

L₈ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, or C₂-C₂₀ alkynyl;

L₉ is C₆-C₁₄ aryl or C₇-C₁₅ aralkyl;

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G_1 is halogen, OR_{21} , SR_{22} , $NR_{23}R_{24}$, $C(=NH)NR_{23}R_{24}$, $NHC(=NH)NR_{23}R_{24}$, $CH=O$, $C(=O)OR_{25}$, $CH(NR_{23}R_{24})(C(=O)OR_{25})$, $C(=O)NR_{23}R_{24}$, a metal coordination group, or a phosphate group;

G_2 is halogen, OH, SH, SCH_3 , or $NR_{23}R_{24}$;

R_{21} is H, C_1 - C_6 alkyl, or a hydroxyl protecting group;

R_{22} is H, C_1 - C_6 alkyl, or a thiol protecting group;

R_{23} and, R_{24} are, independently, H, C_1 - C_6 alkyl, or an amine protecting group;

R_{25} is H, C_1 - C_6 alkyl, or an acid protecting group;

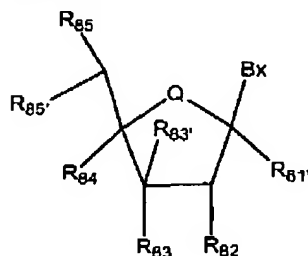
Q is L_1 , G_3 , L_1-G_3 or $G_3-L_1-G_3$;

L_1 is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl;

G_3 is $C(=O)$, $C(=S)$, $C(O)-O$, $C(O)-NH$, $C(S)-O$, $C(S)-NH$ or $S(O)_2$; and

n is 0 or 1.

22. (withdrawn) The composition of claim 1 wherein the sugar surrogate is of the formula:



where:

Bx is a heterocyclic base moiety;

Q is S, O, NH, $N(C_1-C_6 \text{ alkyl})$, CH_2 , CHF, or CF_2 ;

R_{82} is a sugar substituent;

R_{83} and R_{85} are each independently OH, a protected hydroxyl group, an internucleoside linkage to an adjacent monomer, or a terminal group; and

$R_{81'}$, $R_{83'}$, R_{84} and $R_{85'}$ are each independently H, alkyl, aralkyl, or aryl.

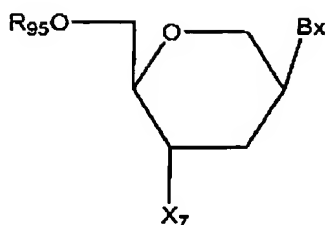
23. (withdrawn) The composition of claim 11 wherein the sugar surrogate is of formula:

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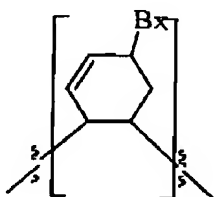
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wherein Bx is a heterocyclic nucleobase, R₉₅ is H, a hydroxyl protecting group, an internucleoside linkage to an adjacent monomer, or a terminal group, and X₇ is a H or a sugar substituent.

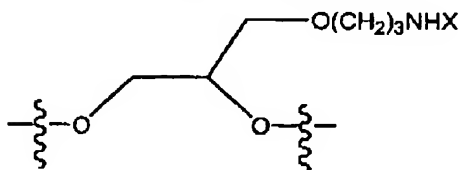
24. (withdrawn) The composition of claim 11 wherein the sugar surrogate is of the formula:



wherein Bx is a heterocyclic base moiety.

25. (withdrawn) The composition of claim 12 wherein the sugar surrogate is a 4'-thioribonucleoside or a 2'-deoxy-4'-thioribonucleoside.

26. (withdrawn) The composition of claim 1 wherein the sugar surrogate comprises at least one monomer of the formula:



wherein X is a conjugate.

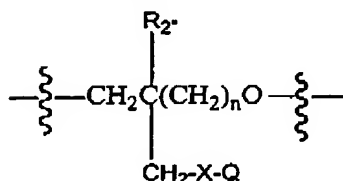
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27. (withdrawn) The composition of claim 1 wherein the oligomer comprises at least one monomer of the formula:



wherein:

R₂ is hydrogen, nitro, lower alkyl amino, diloweralkyl amino or methyl;

X is oxygen, sulfur, or --NR₆;

R₆ is hydrogen or lower alkyl;

n is an integer from 1 to 40;

Q is a heterocyclic base moiety.

28. (currently amended) A composition comprising an oligomer complementary to and capable of hybridizing to a selected target nucleic acid and at least one protein, said protein comprising at least a portion of a RNA-induced silencing complex (RISC), wherein:

said oligomer includes at least one nucleoside having a modification comprising a sugar surrogate wherein said sugar surrogate is a 4'-thioribonucleoside or a 2'-deoxy-4'-thioribonucleoside.

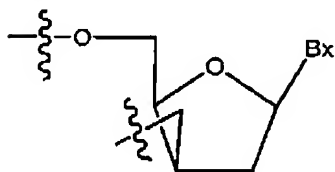
29. (original) The composition of claim 28 wherein said oligomer is an antisense oligomer.

30. (original) The composition of claim 28 wherein said oligomer has 10 to 40 nucleobases.

31. (original) The composition of claim 28 wherein said oligomer has 18 to 30 nucleobases.

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32. (original) The composition of claim 28 wherein said oligomer has 21 to 24 nucleobases.
33. (currently amended) The composition of claim 28 further including a further oligomer, said further oligomer complementary to and ~~hybridizable~~ hybridizable to said oligomer.
34. (original) The composition of claim 33 wherein said further oligomer is a sense oligomer.
35. (original) The composition of claim 33 wherein said further oligomer is an oligomer having a plurality of ribose nucleoside units.
36. (withdrawn) The composition of claim 28 wherein the sugar surrogate is a cyclobutyl nucleoside, cyclopentyl nucleoside, proline nucleoside, cyclohexene nucleoside, hexose nucleoside or a cyclohexane nucleoside.
37. (withdrawn) The composition of claim 28 wherein the sugar surrogate is an arabinonucleoside, xylonucleoside, lyxonucleoside, erythronucleoside, threonucleoside, 4'-thioribonucleoside, or 2'-deoxy-4'-thioribonucleoside.
38. (withdrawn) The composition of claim 37 wherein the sugar surrogate is an arabinonucleoside.
39. (withdrawn) The composition of claim 37 wherein the sugar surrogate is an xylonucleoside of the formula:



where Bx is a heterocyclic base moiety.

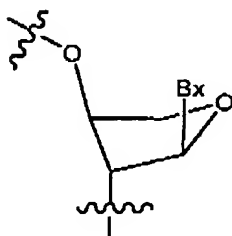
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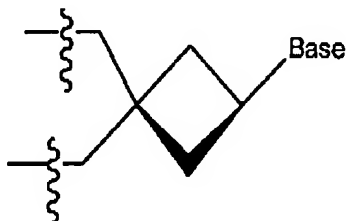
40. (withdrawn) The composition of claim 37 wherein the sugar surrogate is a threonnucleoside of the formula:



wherein Bx is a hetrocyclic base moiety.

41. (withdrawn) The composition of claim 36 wherein the sugar surrogate is a cyclobutyl nucleoside.

42. (withdrawn) The composition of claim 41 wherein the cyclobutyl nucleoside is of the formula:

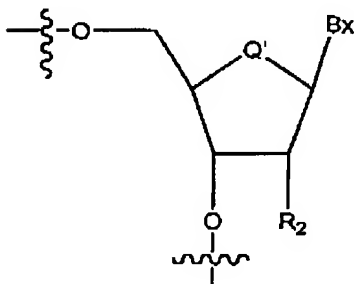


43. (withdrawn) The composition of claim 36 wherein the sugar surrogate is a cyclopentyl nucleoside.

44. (withdrawn) The composition of claim 43 wherein the cyclopentyl nucleoside is of the formula:

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where:

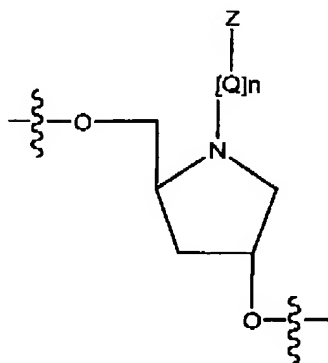
Bx is a heterocyclic base moiety;

Q' is CH₂, CHF, or CF₂; and

R₂ is OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl or alkynyl.

45. (withdrawn) The composition of claim 36 wherein the sugar surrogate is a proline nucleoside.

46. (withdrawn) The composition of claim 45 wherein the proline nucleoside is of the formula:



wherein:

Z is L_8 , L_8-G_1 , L_9 , L_9-G_2 , $NR_{23}R_{24}$, a nitrogen-containing heterocycle, a purine, a pyrimidine, a phosphate group, a polyether group, or a polyethylene glycol group;

L₈ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, or C₂-C₂₀ alkynyl;

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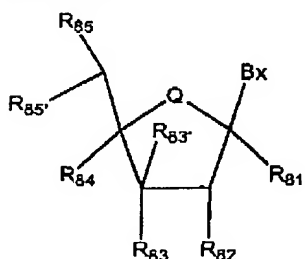
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 L_9 is C_6 - C_{14} aryl or C_7 - C_{15} aralkyl; G_1 is halogen, OR_{21} , SR_{22} , $NR_{23}R_{24}$, $C(=NH)NR_{23}R_{24}$, $NHC(=NH)NR_{23}R_{24}$, $CH=O$, $C(=O)OR_{25}$, $CH(NR_{23}R_{24})(C(=O)OR_{25})$, $C(=O)NR_{23}R_{24}$, a metal coordination group, or a phosphate group; G_2 is halogen, OH, SH, SCH_3 , or $NR_{23}R_{24}$; R_{21} is H, C_1 - C_6 alkyl, or a hydroxyl protecting group; R_{22} is H, C_1 - C_6 alkyl, or a thiol protecting group; R_{23} and R_{24} are, independently, H, C_1 - C_6 alkyl, or an amine protecting group; R_{25} is H, C_1 - C_6 alkyl, or an acid protecting group; Q is L_1 , G_3 , L_1-G_3 or $G_3-L_1-G_3$; L_1 is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl; G_3 is $C(=O)$, $C(=S)$, $C(O)-O$, $C(O)-NH$, $C(S)-O$, $C(S)-NH$ or $S(O)_2$; and n is 0 or 1.

47. (withdrawn) The composition of claim 28 wherein the sugar surrogate is of the formula:

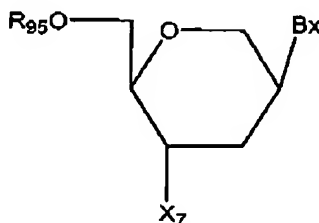


where:

 Bx is a heterocyclic base moiety; Q is S, O, NH, $N(C_1-C_6 \text{ alkyl})$, CH_2 , CHF, or CF_2 ; R_{82} is a sugar substituent; R_{83} and R_{85} are each independently OH, a protected hydroxyl group, an internucleoside linkage to an adjacent monomer, or a terminal group; and $R_{81'}$, $R_{83'}$, R_{84} and $R_{85'}$ are each independently H, alkyl, aralkyl, or aryl.

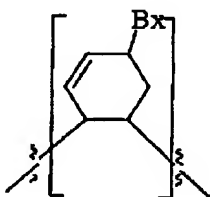
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48. (withdrawn) The composition of claim 36 wherein the sugar surrogate is of formula:



wherein Bx is a heterocyclic nucleobase, R₉₅ is H, a hydroxyl protecting group, an internucleoside linkage to an adjacent monomer, or a terminal group, and X₇ is a H or a sugar substituent.

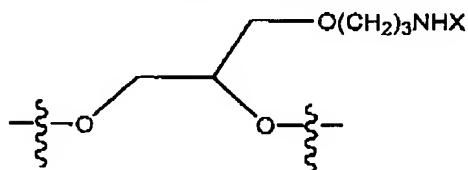
49. (withdrawn) The composition of claim 36 wherein the sugar surrogate is of the formula:



wherein Bx is a heterocyclic base moiety.

50. (withdrawn) The composition of claim 36 wherein the sugar surrogate is a 4'-thioribonucleoside or a 2'-deoxy-4'-thioribonucleoside,

51. (withdrawn) The composition of claim 28 wherein the sugar surrogate comprises at least one monomer of the formula:



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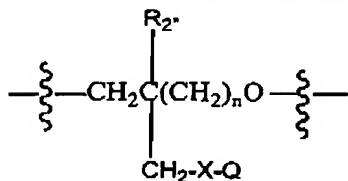
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wherein X is a conjugate.

52. (withdrawn) The composition of claim 28 wherein the sugar surrogate comprises at least one monomer of the formula:



wherein:

R₂ is hydrogen, nitro, lower alkyl amino, diloweralkyl amino or methyl;

X is oxygen, sulfur, or --NR₆;

R₆ is hydrogen or lower alkyl;

Q is a heterocyclic base; and

n is an integer from 1 to 40.

53. (currently amended) An oligomer having at least a first region and a second region, wherein:

said first region of said oligomer complementary to and capable of hybridizing with said second region of said oligomer,
at least a portion of said oligomer complementary to and capable of hybridizing to a selected target nucleic acid,
said oligomer further including at least one nucleoside having a modification comprising a sugar surrogate wherein said sugar surrogate is a 4'-thioribonucleoside or a 2'-deoxy-4'-thioribonucleoside.

54. (original) The oligomer of claim 53 wherein each of said first and said second regions has at least 10 nucleosides.

55. (original) The oligomer of claim 53 wherein said first regions in a 5' to 3' direction is complementary to said second region in a 3' to 5' direction.

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56. (original) The oligomer of claim 53 wherein said oligomer includes a hairpin structure.
57. (original) The oligomer of claim 53 wherein said first region of said oligomer is spaced from said second region of said oligomer by a third region and where said third region comprises at least two nucleosides.
58. (original) The oligomer of claim 53 wherein said first region of said oligomer is spaced from said second region of said oligomer by a third region and where said third region comprises a non-nucleoside.
59. (original) A pharmaceutical composition comprising the composition of claim 1 and a pharmaceutically acceptable carrier.
60. (original) A pharmaceutical composition comprising the composition of claim 28 and a pharmaceutically acceptable carrier.
61. (original) A pharmaceutical composition comprising the oligomeric compound of claim 53 and a pharmaceutically acceptable carrier.
62. (original) A method of modulating the expression of a target nucleic acid in a cell comprising contacting said cell with a composition of claim 1.
63. (original) A method of modulating the expression of a target nucleic acid in a cell comprising contacting said cell with a composition of claim 28.
64. (original) A method of modulating the expression of a target nucleic acid in a cell comprising contacting said cell with an oligomeric compound of claim 53.

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65. (original) A method of treating or preventing a disease or disorder associated with a target nucleic acid comprising administering to an animal having or predisposed to said disease or disorder a therapeutically effective amount of a composition of claim 1.

66. (original) A method of treating or preventing a disease or disorder associated with a target nucleic acid comprising administering to an animal having or predisposed to said disease or disorder a therapeutically effective amount of a composition of claim 28.

67. (original) A method of treating or preventing a disease or disorder associated with a target nucleic acid comprising administering to an animal having or predisposed to said disease or disorder a therapeutically effective amount of an oligomeric compound of claim 53.